PHARMACOTHERAPY

CASE REPORT

In Utero Oxcarbazepine Exposure and Neonatal Abstinence Syndrome: Case Report and Brief Review of the Literature

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Oxcarbazepine is a second-generation antiepileptic drug that is used to treat partial seizures. Although it has been increasingly used in pregnant women, its fetal safety has not been fully validated. We describe a 12-hour-old neonate who developed neonatal abstinence syndrome (NAS) after intrauterine exposure to oxcarbazepine. The neonate was born via cesarean section to a mother who took oxcarbazepine 300 mg/day for treatment of seizures throughout her pregnancy. Approximately 12 hours after birth, the infant developed paroxysmal jitter, which mainly presented as increased excitability, irritability, limb shaking, and increased muscle tone. These symptoms resolved by day 9 of life. Although NAS occurs most often after in utero exposure to opioids, exposure to other drugs during pregnancy may contribute to a small proportion of NAS cases. To our knowledge, this is the second case report of oxcarbazepine-induced NAS. Pregnant women with epilepsy should weigh the pros and cons of continuing oxcarbazepine during their pregnancy when they are prescribed this drug. For infants with in utero oxcarbazepine exposure, comprehensive assessments and examinations are necessary for screening oxcarbazepine-induced NAS.

KEY WORDS Oxcarbazepine, neonatal abstinence syndrome, jitter.
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As a 10-keto analogue of carbamazepine, oxcarbazepine is one of the newer antiepileptic drugs. It has been approved for the treatment of partial seizures as both monotherapy and adjunctive therapy in children and adults and is used for neuropathic pain and mood stabilization. After oral intake, oxcarbazepine is rapidly absorbed and metabolized into its pharmacologically active metabolite, 10-monohydroxy derivative (MHD). To date, it has been increasingly used in childbearing women with epilepsy. Recent studies have suggested that newborns of women receiving oxcarbazepine monotherapy during pregnancy do not show an increased risk for major congenital malformations; however, one case reported an infant with unilateral radius aplasia related to intrauterine lamotrigine and oxcarbazepine exposure.[1–5]

Neonatal abstinence syndrome (NAS) is characterized by signs and symptoms that indicate central nervous system hyperirritability (e.g., increased muscle tone, seizures, tremors, and excessive crying) and dysfunction of the autonomic nervous system (e.g., sweating, fever, and nasal congestion), gastrointestinal tract (e.g., poor feeding, vomiting, diarrhea, and dehydration), and respiratory system (e.g., tachypnea).[6–9]

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NAS generally occurs 48–72 hours after birth following in utero opioid exposure.[9] In addition, barbiturate, benzodiazepine, selective serotonin reuptake inhibitor, and alcohol exposures during pregnancy contribute to a small proportion of NAS cases.[6, 10] This report describes the occurrence of NAS in a 12-hour-old infant after in utero oxcarbazepine exposure.

Case Report

A male infant was born at 40 3/7 weeks of gestation to a G2P1, 29-year-old mother. The mother had been treated for epilepsy with oxcarbazepine for 14 months, with a total daily oral dose of 300 mg (150 mg twice/day); her seizures were well controlled during her pregnancy. Her pregnancy was complicated with gestational diabetes mellitus, and she controlled her blood glucose level through diet and exercise. A history of additional medications, drug abuse, smoking, or alcohol consumption was denied during the pregnancy. The infant was born via cesarean section because of active-phase labor arrest. His birth weight was 3320 g, and his length was 49 cm. On delivery, the Apgar scores were 9 at 1 minute and 10 at both 5 and 10 minutes, indicating good health.

Approximately 12 hours after birth, the infant began to experience paroxysmal jitter, which presented as increased muscle tone, shaking of the lower limbs, and gripping of the hands, with 1–2 seconds of recovery. These symptoms occurred frequently, almost once every few minutes, without perioral cyanosis or fever symptoms. His blood glucose level was 48.6 mg/dl (2.7 mmol/L) at 1 hour, 63 mg/dl (3.5 mmol/L) at 2 hours, 81 mg/dl (4.5 mmol/L) at 3 hours, 68.4 (3.8 mmol/L) at both 6 and 12 hours, and 75.6 mg/dl (4.2 mmol/L) at 24 hours. Routine blood examination was performed before admission and showed a white blood cell count of $25.55 \times 10^3/mm^3$, hemoglobin concentration of 18 g/dl (180 g/L), and a platelet count of $227 \times 10^3/mm^3$. The percentage of lymphocytes was 23.44%, and the C-reactive protein level was 5 mg/L. Cefaclor 62.5 mg twice/day was prophylactically administered for a total of five doses. Cranial ultrasound showed no abnormal features. To confirm the diagnosis and provide further treatment, the infant was transferred to the neonatal intensive care unit (NICU) in our hospital 2 days after birth.

The infant's body temperature on admission was 36.5°C, pulse was 166 beats/minute, respiratory rate was 47 breaths/minute, and blood pressure was 60/34 mm Hg. Physical examination revealed a relatively high muscle tone. Arterial blood gas analysis showed a pH of 7.53, carbon dioxide partial pressure of 20 mm Hg, oxygen partial pressure of 66 mm Hg, base excess level of –6.0 mEq/L, and a bicarbonate level of 16.7 mEq/L. Routine blood tests, liver and kidney function, blood glucose levels, and electrolyte levels were normal. Cardiac enzyme, blood ammonia, lactic acid, and β-hydroxybutyric acid levels were slightly higher on admission. The jitter of the limbs may have been related to perinatal factors (e.g., hypoxia/asphyxia, intracranial hemorrhage), an internal environment disorder (e.g., hypoglycemia, hypocalcemia), intracranial infections, the infant's own factors (e.g., structural or developmental abnormalities of the nervous system, metabolic diseases, epilepsy-related gene mutation), or oxcarbazepine-induced drug withdrawal. The infant did not have any evidence of hypoxia/asphyxia or intracranial hemorrhage in his medical history. In addition, cranial ultrasound results did not support perinatal factors. When considering the infant's normal electrolyte and complete blood count on admission, coupled with no evidence of infection and a physical examination that revealed no neck resistance or nervous system signs, an internal environment disorder and intracranial infection factors were excluded. To exclude the infant's own factors, imaging examinations and metabolic screening were completed. Because the mother had a history of epilepsy, epilepsy-related genes could be detected if necessary. On postnatal day 7, the infant's metabolic screening and head magnetic resonance imaging results revealed no obvious abnormality.

After admission, the infant presented with increased excitability, irritability, limb shaking, and increased muscle tone, which became obvious when the infant was hungry and improved after feeding. Concerned that the infant was exposed to oxcarbazepine in utero, the pediatric pharmacist reviewed the literature and suggested that NAS could not be excluded. Therefore, the Finnegan Neonatal Abstinence Severity Score[11] was determined to evaluate the infant's withdrawal symptoms and whether pharmacologic intervention was needed. The Finnegan score increased from 4 on postnatal day 4 to 9 on postnatal day 6, indicating NAS. A recommendation was made to monitor the oxcarbazepine plasma concentrations of both the mother and

the infant. The oxcarbazepine steady-state peak plasma concentration of the mother was 18.5 mg/L (therapeutic range 3–35 mg/L), and the trough concentration was 16.7 mg/L, whereas the concentration in the infant on postnatal day 6 was 2.6 mg/L. Because three consecutive Finnegan scores averaging 8 or greater, or two scores averaging 12 or greater, did not occur and because the oxcarbazepine concentration of the infant was relatively low, oxcarbazepine was directly discontinued rather than gradually withdrawn from the infant, and no treatment other than supportive care was needed. In terms of feeding, the oxcarbazepine steady-state peak milk concentration of the mother was 7.8 mg/L, consistent with the 0.5 milk : plasma concentration ratio reported in the literature.[12] *HLA-B*1502* genotype testing of the infant was performed by a pharmacist to evaluate the risk of carbamazepine-related toxic effects, which revealed that the infant was *HLA-B*1502* negative. Breastfeeding was not contraindicated for this infant. After weighing the pros and cons, the mother made a final decision to continue breastfeeding.

On postnatal day 7, a decrease in limb shaking movements was observed, although there was no improvement in the increased muscle tone. By day 10 of life, the infant's jitter frequency decreased to one time and was relieved within 2 seconds, thus revealing a significant improvement. The infant was then discharged from the NICU. The parents were told that the in utero oxcarbazepine exposure might lead to a risk of teratogenicity; however, the chance was relatively small. Owing to the mother's relatively low dose of oxcarbazepine, there seemed to be no abnormalities in appearance and in the vital organs of the infant. To evaluate whether oxcarbazepine had an impact on the infant's nervous system and organ development, long-term follow-up was needed.

Discussion

NAS has become an increasingly significant health problem in recent years. In a study evaluating the incidence of NAS in the United States in 2009, infants with NAS were significantly more likely to have seizures (2.3%, SE 0.2%), feeding difficulties (18.1%, SE 0.7%), low birth weight (19.1%, SE 0.5%), and respiratory complications (30.9%, SE 0.7%) compared with other hospital births.[13] According to the data of 28 U.S. states available in the Healthcare Cost and Utilization Project (HCUP) during 1999–2013, the overall incidence of NAS increased by 300%, from 1.5/1000 hospital births in 1999 to 6.0/1000 hospital births in 2013.[14] Mean hospital charges for infants with NAS showed a 35% increase, from $39,400 (95% confidence interval [CI] $33,400–$45,400) in 2000 to $53,400 (95% CI $49,400–$57,700, $P<0.001$) in 2009.[13] The prevalence of NAS was 5.1:1000 live births in Ontario, Canada, in 2011, 2.73:1000 live births in England in 2011, and 2.7:1000 live births in Western Australia in 2009.[15] In China, studies relevant to NAS are rare and mostly case reports, and no exact incidence data have been reported.

NAS occurs most often after in utero exposure to opioids. To our knowledge, this is the second case report of an infant developing NAS following in utero oxcarbazepine exposure. In the first reported case of NAS induced by oxcarbazepine,[16] the infant was born to a mother in status epilepticus who was treated with oxcarbazepine 1400 mg/day as monotherapy. Clinical signs of NAS occurred on the third day of life, peaked on day 7, and normalized by day 12 without any treatment other than supportive therapy. In addition to NAS, cardiac and renal malformations were identified in the infant, and transient hyponatremia was noted. Follow-up at 15 months revealed normal development.

For suspected or known cases of NAS, the Finnegan Neonatal Abstinence Severity Score[11] or the modified Finnegan scale is the most widely used assessment tool to evaluate the signs and symptoms of NAS. The scoring should be started within 2 hours of birth and applied every 2–4 hours for at least 72 hours. Pharmacologic treatments should be initiated when three consecutive scores are ≥ 8, or when the average of two scores or two consecutive scores are ≥ 12. If these criteria are not met, the recommendation is to continue screening and provide nonpharmacologic interventions.

Pharmacologic treatments are required in approximately 60–80% of infants with NAS. However, currently, no universally accepted standard exists with respect to pharmacologic care, and variations exist in current practice. Morphine and methadone are first-line pharmacologic treatments for NAS due to opioid withdrawal, and phenobarbital is the primary choice for the treatment of NAS induced by nonopioid drugs or can serve as an adjunct for neonatal opioid withdrawal.[17, 18] Currently, the consensus is that the use of a standardized institutional protocol based on best practice is more

important than the use of a specific drug for the pharmacologic treatment of NAS.[19] In addition to pharmacologic treatments, other supportive interventions, such as swaddling, breastfeeding, soothing behaviors, positional support, and small and frequent hypercaloric feedings, may be beneficial to relieve the symptoms of NAS.[20] Given the complexity of the disease, the most effective treatment requires a systematic, multidisciplinary, and multimodal approach including physicians, nurses, pharmacists, and sometimes the infant's family members. Once the Finnegan score is < 8 for a minimum of 72 hours or 120 hours for methadone exposure, patients are eligible for discharge. For the infant in this case report, the Finnegan score peaked at 9 on day 6 of life, indicating NAS. Three consecutive NAS scores averaging 8 or greater, or two scores averaging 12 or greater, did not occur; thus, supportive care, rather than pharmacologic interventions, was implemented. Regrettably, the NICU in our hospital did not have standardized screening protocols and training materials for NAS at that time; these protocols will be completed in the near future.

In terms of feeding for infants with NAS, evidence-based reviews strongly recommend breastfeeding, with emerging evidence that favors rooming-in.[21, 22] Studies have shown that breastfeeding by mothers who are taking methadone may lead to the relief of NAS, which presents as a delayed onset of NAS, reduced NAS scores, and a decreased need for pharmacologic treatment.[23, 24] Guidelines from the American Academy of Pediatrics,[25] Academy of Breastfeeding Medicine,[26] and American College of Obstetricians and Gynecologists[27] currently encourage selective breastfeeding in some infants based on the evidence that breast milk can reduce NAS symptoms and minimize pharmacologic treatments.[28] In our infant's case, the NAS was induced by oxcarbazepine, and information about its use during breastfeeding is limited. A case report revealed a low oxcarbazepine milk-to-plasma concentration ratio (0.5) and a low concentration in breast milk (<11 μg/ml), with a low relative infant dose (1.5%-1.7%).[29] The plasma concentrations of oxcarbazepine and 10-hydroxy-carbamazepine were negligible (both <0.2 μg/ml) in the infant. No adverse effects or growth retardation were observed during the 5-year follow-up period. Another case also reported normal growth and development of the breastfed infant during the first month of life while the mother was taking oxcarbazepine.[30] The Hale lactation risk category of oxcarbazepine is L3, which means moderately safe for breastfeeding.[12] In our infant's case, by weighing the potential benefits against the risks, the mother made a final decision to continue breastfeeding. She was told to avoid breastfeeding when oxcarbazepine was at its peak concentration and to observe the infant's muscle tension and mental condition during lactation. After feeding, the infant's excitability and muscle tension were relieved.

Currently, information about the influence of in utero oxcarbazepine exposure on the fetus is quite limited. An infant with micrognatia, low-set ears, facial dysmorphism, and unilateral radius aplasia due to lamotrigine and oxcarbazepine exposure during pregnancy was reported.[5] A prospective cohort concluded that in utero exposure to oxcarbazepine was associated with impaired early language abilities at the age of 7 months.[31] A cohort study that included 2600 children exposed to antiepileptics during pregnancy and 771,412 unexposed children showed that oxcarbazepine had a low risk of major congenital malformation (1.8% for oxcarbazepine monotherapy, odds ratio 0.64, p=0.66).[3] Although the use of oxcarbazepine appeared to be relatively safe, further studies are still needed. Of 262 pregnancies exposed to oxcarbazepine monotherapy in a prospective observational study, the rate of spontaneous abortions and stillbirths was 8.4%, which was similar to those observed for lamotrigine, carbamazepine, valproic acid, levetiracetam, and phenobarbital.[32] To identify oxcarbazepine's long-term adverse reactions and provide timely interventions, long-term growth and neurodevelopmental follow-up of the exposed infants is recommended.

Conclusion

This case report describes an infant exposed to oxcarbazepine in utero who developed symptoms of a withdrawal syndrome, which presented as increased excitability, irritability, limb shaking, and increased muscle tone. To our knowledge, this is the second report of oxcarbazepine-induced NAS. For newborns with in utero oxcarbazepine exposure, a comprehensive workup to screen oxcarbazepine-induced NAS is needed. For suspected or known cases of NAS, timely assessment and a multidisciplinary, protocol-based intervention including doctors, nurses, pharmacists, and family members is important, and long-term follow-up is recommended.

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